REVIEW

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Therapeutic Dilemmas in Mixed Septic-Cardiogenic Shock

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ABSTRACT

Sepsis is an increasing cause of decompensation in patients with chronic heart failure with reduced or preserved ejection fraction. Sepsis and decompensated heart failure results in a mixed septic-cardiogenic shock that poses several therapeutic dilemmas: Rapid fluid resuscitation is the cornerstone of sepsis management, while loop diuretics are the main stay of decompensated heart failure treatment. Whether inotropic therapy with dobutamine or inodilators improves microvascular alterations remains unsettled in sepsis. When to resume loop diuretic therapy in patients with sepsis and decompensated heart failure is unclear. In the absence of relevant guidelines, we review vasopressor therapy, the timing and volume of fluid resuscitation, and the need for inotropic therapy in patients who, with sepsis and decompensated heart failure, present with a mixed septic-cardiogenic shock.

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INTRODUCTION

After cancer, chronic heart failure is the most common comorbidity in hospitalized patients for sepsis, and two-thirds of patients in cardiac intensive care with sepsis have preexisting heart failure.[1,2] Sepsis is a common cause of decompensation and accounts for more than half of noncardiovascular deaths in heart failure with reduced ejection fraction.[3-7] Patients who are septic with preexisting heart failure with preserved ejection fraction or right ventricular failure have a poor outcome.[8,9] Sepsis-induced cardiomyopathy refers to the development of left ventricular, biventricular, or right ventricular dysfunction in patients with sepsis.[9-12] Sepsis-induced cardiomyopathy portends a poor outcome for full recovery in surviving patients. Nevertheless, sepsis-induced cardiomyopathy poses the same therapeutic dilemmas that sepsis and decompensated heart failure do.

The increasing incidence of sepsis in patients with preexisting heart failure is changing the epidemiology of shock in cardiac intensive care units. The cause of shock is becoming mixed, septic-cardiogenic rather than solely cardiogenic. We review the therapeutic dilemmas raised by mixed shock in patients with sepsis and decompensated heart failure.

RECOGNITION AND EVALUATION OF SEPSIS AND DECOMPENSATED HEART FAILURE

Patients with decompensated heart failure commonly present with systemic hypotension and normal temperature that can mask sepsis. Decompensated heart failure accounts for systemic hypotension, and normal temperature may in fact mean febrile in patients with chronic heart failure who at baseline can be hypothermic.[13] Blood cultures should be obtained in patients with unexplained heart failure decompensation. Positive blood cultures uncover the mixed nature of the shock state. Central venous oxygen saturation obtained for assessing cardiac output may unexpectedly

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uncover sepsis when >60%-70% in patients with decompensated heart failure. In contrast to sepsis where central venous pressure monitoring does not reliably guide fluid resuscitation, central venous oxygen saturation monitoring helps guide positive inotropic therapy in patients with sepsis and decompensated heart failure.[14] Monitoring heart rate, blood pressure, arterial oxygen saturation, respiratory rate, temperature, urine output, and laboratory tests, including serum lactate and brain natriuretic peptide levels, helps assess the response to therapy.

CLINICAL SIGNIFICANCE

- It is crucial to obtain a blood culture in a patient with acutely decompensated heart failure without overt precipitating factors.
- Adjusted rather than fixed volume and rate of fluid resuscitation should be followed in patients who are septic and have decompensated heart failure.

VASOPRESSOR THERAPY

Fluid resuscitation therapy is mandatory in sepsis and septic shock. The initiation of vasopressor therapy partly depends on the blood pressure response to fluid resuscitation. Prompt vasopressor therapy needs to be initiated early in patients with sepsis and decompensated heart failure who are likely to be fluid overloaded.[15-17]

Norepinephrine, a strong alpha-1 and mild beta-1 adrenergic receptor agonist, is the most commonly used vasopressor agent in all types of shock.[18] Norepinephrine increases systolic and diastolic blood pressure and is the preferred vasoactive agent in sepsis and septic shock.[19,20] Norepinephrine is also the first-line vasoactive agent in mixed shock like sepsis-induced cardiomyopathy with the caveat that alpha-adrenergic receptor stimulation increases cardiac afterload and, thereby, may reduce cardiac output while it enhances right ventricular systolic performance (Figure).[10,12]

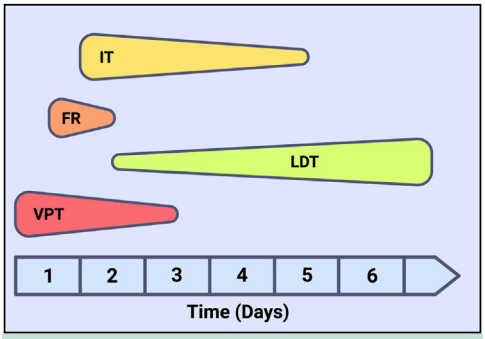

Figure Time course of therapy in mixed shock. Prompt initiation of intravenous vasopressor therapy (VPT) to be tapered and discontinued by day 3-4. Aggressive fluid resuscitation (FR) in patients with weak blood pressure response to vasopressor therapy. Intravenous inotropic therapy (IT) within the first day to help weaning from vasopressor therapy and enabling of loop diuretic therapy (LDT). Initiation of loop diuretic therapy on day 2 to prevent positive fluid balance with up-titration over following days to achieve euvolemic state.

Epinephrine like norepinephrine stimulates alpha- and beta-adrenergic receptors.[21] Epinephrine is a second-line vasopressor agent in sepsis and septic shock because it may decrease splanchnic perfusion, promote ventricular and atrial arrhythmias, increase lactate levels, and is associated with increased incidence of refractory shock.[22-24] A 15-year-old trial failed to uncover safety and efficacy differences between epinephrine alone and norepinephrine plus dobutamine in patients with septic shock.[25] However, a recently reported 3-fold increase of sudden death in patients with cardiogenic shock receiving epinephrine argues against its use as a first-line vasopressor agent in mixed shock.[26,27] However, patients with septic shock and predominant severe right ventricular dysfunction may benefit from initiation of epinephrine as a first-line vasopressor agent.[28]

Vasopressin promotes vasoconstriction by stimulating vasopressin receptor 1A in vascular smooth muscle cells.[29] Endogenous levels of vasopressin tend to be low in sepsis.[30] Vasopressin may restore norepinephrine pressor effects in acidosis and hypoxic conditions.[31] Terlipressin is a long-acting synthetic analogue of vasopressin with higher selectivity for vasopressin receptor 1 than vasopressin.[32] Low-dose terlipressin plus norepinephrine may prevent renal injury and arrhythmias compared with norepinephrine alone in septic shock.[33,34]

Dopamine at infusion rates of 10-20 μg/kg/min acts as a vasopressor through stimulation of alpha-1 adrenergic receptor.[35] When infused at vasoconstrictor rates. dopamine has adverse events like tachycardia, arrhythmias, and death that preclude its use in septic or cardiogenic shock.

FLUID RESUSCITATION

The Centers for Medicare and Medicaid Services (CMS) mandate fluid resuscitation with crystalloid solution at an infusion rate of 30 mL/kg over 3 hours in sepsis and septic shock.[17] Ten-year-old reports of increased in-hospital mortality in patients with sepsis and positive fluid balance led to question the safety of CMS's mandated rapid fluid resuscitation in sepsis, especially in patients with preexisting fluid overload.[36,37] Recent retrospective analysis of Medicare claims data and single-center experiences indicate that CMS-mandated fluid resuscitation does not increase in-hospital mortality or the use of mechanical ventilation in patients with sepsis and preexisting heart failure.[38-42] To the contrary, noncompliance with CMS-mandated fluid resuscitation may increase in-hospital mortality, whereas compliance with CMS-mandated fluid resuscitation reduces intensive care duration in patients with sepsis and preexisting heart failure.[43,44]

An analysis of 1,801 patients from the Multi-parameter Intelligent Monitoring in Intensive Care III database

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uncovers that the fluid accumulation index estimated as the ratio of fluid balance over fluid intake affects in-hospital mortality in patients with sepsis and preexisting heart failure, whereas fluid balance and fluid intake do not.[45] A negative fluid accumulation index has no effect on in-hospital mortality, which only increases when fluid accumulation index is greater than 0.42. Thus, adjusted rather than fixed volume fluid resuscitation may be preferred in patients with sepsis and preexisting heart failure.[45]

Compliance to CMS-mandated fluid resuscitation was lower in patients with preexisting heart failure than with end-stage renal disease or obesity among 847 hospitalized patients for sepsis at Yale Medical Center.[46] Compliance with CMS-mandated fluid resuscitation while reducing the intensive care length of stay did not affect in-hospital mortality in patients with sepsis and preexisting heart failure.[46] Only 10% of patients with preexisting heart failure or end-stage renal disease received CMS-mandated fluid resuscitation in a meta-analysis of 5 fluid resuscitation studies comprising 5,260 patients with sepsis.[47] Aggressive fluid resuscitation resulted in nonstatistically significant increased odds of mortality.[47] Nearly 60% of patients with septic shock who do not receive CMS-mandated resuscitation have chronic heart failure at Mount Sinai medical centers in New York City.[48] The heightened occurrence of volume-associated complications in women may be related to the more aggressive fluid resuscitation for sepsis in women than men.[49]

In brief, while a one-size-fits-all approach may benefit patients with sepsis without preexisting fluid overload, adjusting volume and rate of fluid resuscitation may be a safer approach in patients with sepsis with preexisting heart failure.

When to restart loop diuretic therapy is a critical issue in patients with sepsis and preexisting heart failure because a persistent positive fluid balance heralds a poor outcome in sepsis.[36] Only 1 study dealt with the issue.[50] Restarting loop diuretics therapy within 48 hours of intensive care was safe and shortened the duration of mechanical ventilation compared to a late restart (>48 hours). The relationship between elevated brain natriuretic peptide levels and high mortality in patients with resolving sepsis provides further support for the early restart of loop diuretics therapy in patients with sepsis and preexisting heart failure.[51]

INOTROPIC THERAPY

A low cardiac output as evidenced by mixed or central venous oxygen saturation less than 50% impairs oxygen delivery to essential organs in patients with reduced ejection fraction heart failure and, thus, underlines the need for inotropic therapy with dobutamine or inodilators to improve cardiac output and oxygen delivery.[52] The situation is different in patients with sepsis and septic shock where cardiac output is high due to marked arterial vasodilation, and peripheral oxygen extraction is impaired due to microvascular dysfunction as in part reflected by an elevated mixed or central venous oxygen saturation.[18,53] Blood flow heterogeneity with perfused and nonperfused areas in close vicinity embodies microcirculation alterations in sepsis.[54] In sepsis and septic shock, without myocardial dysfunction, low-dose dobutamine aims at improving capillary perfusion by alleviating microvascular dysfunction and thereby facilitating peripheral oxygen extraction.[55,56]

Whether inotropic therapy with dobutamine is beneficial in sepsis and septic shock is unclear. Dobutamine reduced microvascular blood flow heterogeneity and enhanced oxygen utilization by intestinal villi.[57,58] Conversely, dobutamine did not improve microcirculation and gastrointestinal perfusion in patients with severe sepsis.[59,60] Further, the beneficial effect of dobutamine on the microcirculation may not be hemodynamic but anti-inflammatory through reduced leucocyte-endothelial adhesion in postcapillary venules.[61]

Dobutamine alone or in combination with norepinephrine did not improve oxygen delivery and outcome in critically ill patients with sepsis/septic shock.[62] However, the combination of norepinephrine and dobutamine reduced the 28-day mortality compared with any other vasoactive agents in a meta-analysis of 43 trials comprising 5,767 patients with sepsis or septic shock.[20] Conversely, the 121 patients who received dobutamine did not fare better than the 2,165 who did not in a recent propensity score-matched analysis of 2,826 patients with sepsis.[63]

A standard recommendation in patients with sepsis and preexisting heart failure with reduced ejection fraction is combined administration of norepinephrine and low-dose dobutamine (<5 μg/kg/min) to maintain mixed or central venous oxygen saturation greater than 70% until the systemic inflammatory response abates.[64,65] Administration of dobutamine at higher doses may cause myocardial injury and inflammatory-mediated tissue damage.[66] Once fluid resuscitation, vasopressors, and antibiotics therapy have lessened the systemic inflammatory response and arterial vasodilatation, patients with sepsis/septic shock and preexisting heart failure with reduced ejection fraction may benefit from dobutamine for few more days until sepsis-induced myocardial depression resolves and patients return to a euvolemic state.[10,12,67]

Patients with sepsis and preexisting heart failure with preserved ejection fraction have a high cardiac output due to marked arteriolar vasodilatation. They do not require inotropic therapy with dobutamine unless they develop sepsis-induced cardiomyopathy or right ventricular failure due to pulmonary hypertension. However, despite a normal or near normal left ventricular ejection fraction, patients with preserved ejection heart failure have variable degrees of myocardial left ventricular systolic dysfunction as assessed by global longitudinal strain using 2-dimensional speckle-tracking echocardiography.[68,69] Assessment of global longitudinal strain is nowadays a semi-automatic function in most commercially available ultrasound systems. Sepsis-induced cardiomyopathy can now be diagnosed and monitored by serial measurements of global longitudinal strain in patients with normal left ventricular ejection fraction.[70] Of great clinical interest, myocardial left ventricular

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systolic function measured as global longitudinal strain by speckle-tracking echocardiography is an independent predictor of mortality in patients with sepsis and septic shock, whereas left ventricular ejection fraction is not.[71,72] Whether inotropic therapy will improve the prognosis of patients with sepsis and marked myocardial left ventricular systolic dysfunction remains to be investigated.

Levosimendan exerts a positive inotropic action by binding to troponin C during systole and sensitizing the myocardium to calcium.[21] Levosimendan has also a vasodilatory action by opening the adenosine triphosphate sensitive potassium channels in vascular smooth muscle cells.[21] Not depending on the production of cyclic adenosine monophosphate, the positive inotropic action of levosimendan carries a low risk of arrhythmias and resistance to catecholamines.[73] Levosimendan is cardioprotective by opening mitochondrial adenosine triphosphate-sensitive channels in cardiac muscle.[74] Levosimendan improves tissue perfusion/oxygenation and reduces the release of pro-inflammatory cytokines in patients with sepsis.[75,76] In an experimental model of hypotension, levosimendan improves the microcirculation[77] and exerts a greater effect on cardiac index and blood lactate than dobutamine but has similar effect on mortality and left ventricular ejection fraction.[78] When added to standard treatment, levosimendan does not improve organ dysfunction and mortality in patients with sepsis.[79] Patients with elevated right ventricular pressures may particularly benefit from levosimendan.[73] Overall, levosimendan yielded contradictory findings in sepsis and septic shock and had no definitive mortality benefit.[64]

The safety and efficacy of milrinone and dobutamine may be similar in acutely decompensated heart failure and cardiogenic shock.[52,80] However, the potent vasodilatory action of milrinone may hinder its effectiveness in patients with sepsis who require vasopressor therapy to maintain a mean blood pressure greater than 65 mm Hg. Further, milrinone, a phosphodiesterase 3 inhibitor, may increase cyclic guanosine monophosphate levels in vascular smooth muscle cells and result in marked hypotension due to high expression of inducible nitric oxide synthase in sepsis.[81]

CONCLUSION

In conclusion, management of mixed septic-cardiogenic shock as in patients with sepsis and decompensated heart failure is a balancing act between reversal of microvascular dysfunction with aggressive fluid resuscitation and avoidance of persistent fluid overload in patients with limited cardiac reserve. Therapeutic success depends on a judicious assessment of the relative contribution of systemic inflammation and microcirculatory dysfunction versus cardiac decompensation and end-organ failure to the shock state. Rapid fluid resuscitation and antimicrobial therapy are critical when sepsis plays the larger role and temporary inotropic/mechanical circulatory support may be considered when heart failure decompensation is the predominant issue.

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